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09/380,337	03/06/2000	SETTARA CHANDRASEKHARAPPA	15280-315100	2491

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/380,337	Chandrasekharappa et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) *9-18, 27-29, 34, and 35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 19-26, 30-33, 36, and 37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
18) ☒ Interview Summary (PTO-413) Paper No(s). 15
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-8, 19-26, 30-33, and 36-37 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the invention is drawn to the same special technical feature. This is not found persuasive because while the invention may have a common linking special technical feature, for example, isolation and identification of a mutation in MEN1 which correlates to cancer, the invention contains different categories of invention:

An international and a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

In the instant case, Group I contains a product (a MEN1 polynucleotide) and a process of use of said product (identification of mutations in an MEN1 gene). The inventions of Groups II-V are drawn to different categories of invention (a protein, an antibody, a method of detecting menin in a human cell or tissue sample and corresponding kit, and an organism), and thus the application lacks unity of invention.

It is further noted that it appears claims 28 and 29 should be dependent from claim 27, and are inadvertently recited as dependent from claim 25. Thus the claims are drawn to a non-elected invention and have been removed from Group I (see interview summary, attached)

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-37 are pending in the application. Claims 9-18, 27-29, and 34-35 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-8, 19-26, 30-33, and 36-37 are considered herein.

Claim Objections

2. Claims 19, and 36 are objected to because of the following informalities:

Claim 19 is missing an article in line 3. It appears that "the presence or absence of MEN1 allele" should read "the presence or absence of a MEN1 allele".

In claim 36, it appears that the nucleic acid which is operably linked to a promoter also comprises a nucleic acid encoding a menin polypeptide, however it appears that the claim should recite that the expression cassette comprises a nucleic acid encoding a menin polypeptide.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-8, 19-26, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 are unclear in the recitation of "associated with". The metes and bounds of a nucleic acid "associated with" the presence of multiple endocrine neoplasia type 1 cannot be determined. It is not clear what would be considered a nucleic acid which is "associated with" the presence of multiple endocrine neoplasia type 1 and what would not.

Claims 19-23 and 25-26 are unclear in the recitation of a nucleic acid sequence "essentially encoding" human menin. The metes and bounds of a nucleic acid sequence "essentially encoding" human menin cannot be determined. It is not clear what would be considered a nucleic acid sequence "essentially encoding" human menin and what would not.

Claims 19-23 are unclear in the recitation of a sequence "competent to discriminate between". The metes and bounds of a sequence "competent to discriminate between" cannot be determined. It is not clear what would be considered a sequence "competent to discriminate between" and what would not.

Claim 24 is unclear in the recitation of a sequence "corresponding to" the wild type allele. The metes and bounds of a sequence "corresponding to" the wild type allele cannot be determined. It is not clear what would be considered sequence "corresponding to" the wild type allele and what would not.

Claim 31 is unclear in the recitation of "stringent conditions". The metes and bounds of "stringent conditions" cannot be determined. It is not clear what conditions would be considered "stringent" and what would not.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 5, 8, 24-26, 30-33, and 36-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding the protein of SEQ ID NO:2, or a polynucleotide comprising SEQ ID NO:1 or 3, does not reasonably provide enablement for any polynucleotide "associated with the presence of multiple endocrine

neoplasia type 1" which encodes a protein which has a molecular weight of about 67.5, and binds to an antibody raised against a sequence set forth in SEQ ID NO:2 or has at least 60% or about 80% homology to SEQ ID NO:2, or hybridizes to SEQ ID NO:1, the corresponding vectors, host cells, and kits. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to any polynucleotide "associated with the presence of multiple endocrine neoplasia type 1" which encodes a protein which has a molecular weight of about 67.5, and binds to an antibody raised against a sequence set forth in SEQ ID NO:2 or has at least 60% or about 80% homology to SEQ ID NO:2, or hybridizes to SEQ ID NO:1, the corresponding vectors, host cells, and kits.

It is noted that molecular weight measurements are well established in the art to be highly variant, and only the most rudimentary of descriptive factors with regard to protein identity. It is further noted that a protein which specifically binds to an antibody bound by another protein could be any number of proteins, as numerous antibodies exhibit non-specific binding, or bind to

regions which are common in an innumerable amount of proteins. Thus the claims are broadly drawn, described only by limitations which encompass innumerable polynucleotides.

The specification discloses only SEQ ID NO:1-3, which are menin proteins, and further discloses specific mutations in menin proteins which generally result in increased likelihood of multiple endocrine neoplasia.

Thus the claims encompass numerous polynucleotides, including polypeptides which are yet undiscovered, while the disclosure teaches only three. The claimed polynucleotide could be literally any polynucleotide, provided only that it minimally encodes a polypeptide which has an approximate molecular weight (well known in the art to be variant) of 67.5 Kda, and which binds to an antibody bounds by the disclosed polypeptide. The specification fails to provide guidance as to the structural properties which characterize the broadly claimed polynucleotides.

Thus the specification asserts but does not provide support for a plurality of polynucleotides, which would allegedly result in retained diagnostic function. The nucleic acid sequence of a polynucleotide determines the structural and functional properties of the protein which it encodes, and predictability of which nucleic acids can be substituted within a polynucleotide's sequence and still result in similar activity is extremely complex, and well outside the realm of experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. The specification fails to address that mere conformational similarity (as would be exhibited by proteins bound by the same antibody) does not indicate that polypeptides have similar activity. In fact, a single region on a polypeptide could be similar to

the instantly disclosed polypeptide, and would meet the limitations of the claims. Furthermore, while recombinant techniques are available, it is not routine to screen large numbers of polynucleotides and proteins with the expectation of retaining diagnostic functionality, when specific mutations are only are expected to provide such results. The following is set forth to establish the unpredictability of substitutions in an encoded protein:

Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular

Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Thus the disclosure of three mutate menin peptides is insufficient support under the first paragraph of 35 U.S.C 112 for claims which encompass any and all menin peptides, including those yet undiscovered. The courts have held that:

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his

contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970)

Therefor one of skill in the art would not be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 19-23, 30, 33, and 36-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Nakamura et al., US Patent 5,559,023.

Nakamura et al. teaches a method of detecting the presence or absence of a mutation in a nucleotide sequence essentially encoding a human menin comprising contacting a sample suspected of containing a gene missing MEN1 with an oligonucleotide which is competent to discriminate between wild type menin and mutated menin, and detecting the duplex between the gene and the oligonucleotide. Nakamura et al. further teaches that the oligonucleotide can bind to mutant MEN1 and not wild type, that a portion of the wild type intron can be multiplied using a PCR primer, and allelic specific PCR (column 5, line 45-column 6, line 50). Nakamura et al. also teaches a transfected cell (including animal cells, which would inherently include human cells), comprising a nucleic acid encoding human MEN1, and the corresponding expression cassette and vector. (Column 4, line 24-column 5, line 12)

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thakker et al., Serono Symp., Raven Press, Hereditary Tumors, 1991, pages 77-88, or Bystron et al., PNAS Vol. 87, pages 1968-1972, March 1990, in view of Fulton, US Patent 5,736,330, or Sambrook, Molecular Cloning, chapter 14, pages 14.1-14.35, 1989.

Thakker et al. teaches that mutations in the MEN1 gene are correlated to increased incidence of multiple endocrine neoplasia.

Bystron et al. teaches that mutations in the MEN1 gene are correlated to increased incidence of multiple endocrine neoplasia.

Thakker et al. and Bystron et al. fail to teach methods of detecting these mutations comprising contacting a sample suspected of containing a gene missing MEN1 with an oligonucleotide which is competent to discriminate between wild type menin and mutated menin, and detecting the duplex between the gene and the oligonucleotide. And further fail to teach that the oligonucleotide can bind to mutant MEN1 and not wild type, that a portion of the wild type intron can be multiplied using a PCR primer, and allelic specific PCR.

Methods of using oligonucleotides and PCR to detect mutations are well known in the art. For example, Fulton et al., US Patent 5,736,330 teaches that oligonucleotides and PCR, including allelic specific PCR are useful for detecting mutations, including MEN1 mutations (see column 3, line 25-column 7, line 10). Further, Sambrook et al. also teaches that oligonucleotides and

PCR, including allelic specific PCR are useful for detecting mutations (see entire document, especially page 14.11).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the art known oligonucleotide and PCR techniques exemplified in Fulton and Sambrook to detect MEN1 mutations, and one would have been motivated to do so because MEN1 mutations increase incidence of multiple endocrine neoplasia, as taught by Thakker et al. and Bystron.

11. Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura et al., US Patent 5,559,023, or Thakker et al., Serono Symp., Raven Press, Hereditary Tumors, 1991, pages 77-88, or Bystron et al., PNAS Vol. 87, pages 1968-1972, March 1990, in view of Sambrook et al., Molecular Cloning, Chapter 16, pages 16.1-16.81, 1989.

Thakker et al. teaches that mutations in the MEN1 gene are correlated to increased incidence of multiple endocrine neoplasia.

Bystron et al. teaches that mutations in the MEN1 gene are correlated to increased incidence of multiple endocrine neoplasia.

Thakker et al. and Bystron et al. fail to teach the corresponding vector and transformed cells.

Methods of transforming cells, including human cells using expression cassettes, and expression vectors are well known in the art, and are used to produce recombinant polypeptide, as exemplified in Sambrook et al. (see entire document, especially page 16.3 and 16.10).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the art known techniques of transforming cells and generating expression cassettes and expression vectors using the MEN1 polynucleotides taught in Thakker et al. and Bystron et al., and one would have been motivated to do so to generate polypeptide, which can be used to raise antibodies or test samples, as taught by Sambrook et al, chapter 16.

12. Claims 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thakker et al., Serono Symp., Raven Press, Hereditary Tumors, 1991, pages 77-88, or Bystron et al., PNAS Vol. 87, pages 1968-1972, March 1990, in view of Fulton, US Patent 5,736,330, or Sambrook, Molecular Cloning, chapter 14, pages 14.1-14.35, and chapter 16, pages 16.1-16.81, 1989.

Nakamura et al., and Thakker et al. and Bystron et al. in view of Fulton or Sambrook, chapter 14 and 16 teach as set forth supra.

Nakamura et al., and Thakker et al. and Bystron et al. in view of Fulton or Sambrook, chapter 14 and 16 fail to teach oligonucleotide kits to detect MEN1 mutations.

However it is *prima facie* obvious to package known components into a kit and one is motivated to do so for the purpose of convenience and marketability.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

December 13, 2001

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER